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09/479,877	01/10/2000	MARCIK. WOLF		3642

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	PAPER NUMBER

1645

DATE MAILED: 05/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

USAMRMC
STAFF JUDGE ADVOCATE
FORT DETRICK, MD

2002 MAY 20 AM 8:25

Office Action Summary

Application No.
09/479,877

Applicant(s)

Wolf

Examiner

Portner

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on Feb 25, 2002

2a) This action is FINAL. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) Claim(s) 4-7 and 14-17 is/are pending in the application.

4a) Of the above, claim(s) 4 and 5 is/are withdrawn from consideration.

5) Claim(s) _____ is/are allowed.

6) Claim(s) 6, 7, and 14-17 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claims 4-7 and 14-17 are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some* c) None of:

1. Certified copies of the priority documents have been received.

2. Certified copies of the priority documents have been received in Application No. _____.

3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) The translation of the foreign language provisional application has been received.

15) Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892)

4) Interview Summary (PTO-413) Paper No(s). _____

2) Notice of Draftsperson's Patent Drawing Review (PTO-948)

5) Notice of Informal Patent Application (PTO-152)

3) Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

6) Other: _____

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DETAILED ACTION

Claims 8-13 have been canceled.

Claims 4-7 and 14-17 are pending.

Claims 6-7, 14-17 are elected and under consideration.

Sequence Compliance

1. The instant Specification is now in sequence compliance.

Election/Restriction

2. Claims 4-5 (still pending), and 8-12 (canceled) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Groups I and II, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 13.

3. Applicant's election with traverse of Group III, claims 6-7 and 14-17 in Paper No. 13 is acknowledged. The traversal is on the ground(s) that Applicant traverses the election restriction requirement. This is not found persuasive because each group of claims defines an independent and distinct invention, for reasons of record in paper number 11. The requirement is still deemed proper and is therefore made FINAL.

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Specification

4. The disclosure is objected to because of the following informalities: At page 23, of the specification, SEQ #6 is shown and designated to have 146 amino acids. What is shown is a sequence with 167 amino acids, not 146. Correction of the numbering for the shown sequence is requested.

Claim Rejections - 35 U.S.C. § 101

5. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 6 and 14 are not directed to an isolated and purified protein; the claim reads on a product of nature. The claimed invention is directed to non-statutory subject matter.
7. Claims 7 and 15 are not directed to compositions of matter that evidence the hand of man, in light of the protein and peptide of a protein would exist in nature in the natural host cell which would be considered a type of carrier for the protein or peptide. This rejection could be obviated by amending the independent claims to recite --isolated and purified-- or --recombinant--.

Claim Rejections - 35 U.S.C. § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 6-7 and 17 (vaccine claim dependent upon claims 6-7) and claims 14-16 (claim 16 being a vaccine claim dependent upon claims 14 and 15) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the production of protein and peptides that can be formulated into immunogenic compositions for the stimulation of an immune response, does not reasonably provide enablement for the utilization of any peptide fragment of a protein that shares homology (at least 60% with SEQ ID No 10), or any CS6:CssB subunit for induction of a protective immune response. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification fails to teach how to formulate and use the claimed vaccines. The term "vaccine" encompasses the ability of the specific antigen to induce protective immunity against infection or disease induction, or the treatment of pre-existing disease. The specification teaches immunogenic CS6 subunits, specifically CSSB of 16 kDa, and immunoreactivity of the protein/peptide with

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antibodies, but does not show that upon administration of the protein/peptide to an animal, that the composition induces a lasting immune response that is protective against challenge. The specification suggests that the protein may play a significant role as a vaccine.

The specification does not provide substantive evidence that the claimed vaccines are capable of inducing protective immunity. This demonstration is required for the skilled artisan to be able to use the claimed vaccines for their intended purpose of preventing infections caused by ETEC strains of E.coli. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines, i.e. would not be able to accurately predict if protective immunity has been induced.

The ability to reasonably predict the capacity of a single bacterial immunogen to induce protective immunity from in vitro antibody reactivity studies is problematic. Ellis exemplifies this problem in the recitation that "the key to the problem (of vaccine development) is the identification of the active protein component of a virus or microbial pathogen that itself can elicit the production of protective

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antibodies"(page 572, second full paragraph). Unfortunately, the art is replete with instances where even well characterized antigens that induce an in vitro neutralizing antibody response fail to elicit in vivo protective immunity. See Boslego et al. wherein a single gonococcal pilin protein fails to elicit protective immunity even though a high level of serum antibody response I s induced (page 212, bottom of column 2). Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful vaccine without the prior demonstration of vaccine efficacy.

The specification fails to teach the identity of homologs of the protein/peptide of SEQ ID NO 10 that are able to induce a protective immune response. Further, the specification fails to provide an adequate written description of what the sequences or sources of the claimed homolog peptides are that would serve as vaccine peptides upon administration to an immunocompetent host.

The skilled artisan would be required to de novo locate, identify and characterize the claimed homolog proteins, proteins and peptides that would serve

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to induce a protective immune response in view of the unpredictability in the art of inducing a protective immune response which administering a composition that contains only a single bacterial protein or peptide. This would require undue experimentation given the fact that the specification is completely lacking in teachings as to other surface proteins with the claimed characteristics.

11. Claims 14-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (scope). This is a *written description rejection*.

The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing.

The claimed invention is directed to a peptide of protein containing (comprising) a sequence at least 60% homology with SEQ ID NO 10. What all of the peptides of protein that share 60% homology over any amino acid sequence of SEQ ID NO 10, and may evidence any biological function has not been described in clear conscience terms as to convey that the

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claimed genus of peptides were in possession by Applicant at the time of filing and have not been described.

The specification discloses CS6, subunits CssA, CssB, CssC and CssD from ETEC pathogenic E.coli, and the elected invention being directed to SEQ ID NO 10 that codes for CssB obtained from Ecoli strain E8775. The claims, as written, however, encompass bacterial peptides of proteins that comprise alterations and are not obtained from the beta subunit of an ETEC colonization factor IV protein. The claimed genus of peptides of a protein have not been described.

A description of a genus may be achieved by means of a recitation of a representative species, falling within the scope of the genus or of a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398-1412, 1406 (Fed. Cir. 1997).

The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of peptides that have only a sequence of amino acids that share 60% homology with SEQ ID NO 10. There is no description of what or how many amino acids are in the claimed peptides that comprise additional amino acids, in addition to the sequence that shares homology with SEQ ID NO 10. The specification proposes to discover other members of the genus by using sequence

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homologies and introduction of alterations based upon what is already known. There is no description, however, of what these alterations are structurally.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that “applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the ‘written description’ inquiry, *whatever is now claimed*.” (See page 1117). The specification does not “clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.” (See *Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Sufficient support for the generic claims has not been provided. See the Interim Guidelines on Written Description, (Fed Reg , June 15, 1998, Volume 63, Number 114, pages 32639-32645) and the Revised Interim Guidelines for the Examination of Patent Applications

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Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

12. Claims 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14-16 recites the phrase "wherein in all instances the substitutions are conservative". Homology is not limited to only substitutions in an amino acid sequence. Homology defines an evolutionary relationship between molecules that are obtained from different strains, species and sources (see Reeck et al and Lewin, 1987). The claimed peptide of protein is not limited to a peptide that only evidences conservative substitutions in SEQ ID NO 10, but is directed to a peptide of a protein that comprises any size sequence ("containing a sequence") selected from SEQ ID NO 10 that shares 60% homology with a sequence selected from SEQ ID No 10. JP06062866 discloses a sequence that shares 100% identity with a sequence of amino acids of SEQ ID NO 10 over 7 amino acid and comprises additional amino acids to result in a protein from C. glutamicum beta subunit (see sequence alignment provided). The combination of claim limitations relative to the word "homology" and "substitutions are conservative" does not distinctly claim Applicant's invention. What biological function does the

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claimed peptide homolog have that evidences only 60% homology with a sequence of amino acids from SEQ ID NO 10? Clarification of the claimed peptide of a protein is requested.

Claim 16 is directed to a vaccine that contains a “peptide of a protein containing a sequence” from SEQ ID NO 10. What is the sequence from SEQ ID NO 10 that will induce a protective immune response and function as a vaccine? How big is the sequence that defines the peptide selected from SEQ ID NO 10? If the peptide is only 10 amino acids and 6 are identical with SEQ ID NO 10 (60% homology) then, what is the protein that only shares 6 amino acids with SEQ ID No 10 and would function as a vaccine?

Claim Rejections - 35 U.S.C. § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 6-7, 17 and 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by McConnell et al (1988).

The claimed invention is directed to a protein or peptide comprising SEQ ID No 10, a sequence present in E8775 CS6 antigen from E.coli.

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(Claim 6 and 14) McConnell et al disclose an isolated protein/peptide E8775 CS6 antigen from E.coli, wherein two bands were found with molecular masses of 14.5 and 16.0 kDa in a SDS-PAGE gel. The reference does not disclose the amino acid sequence of the protein but the source of the protein is the same as that used to obtain SEQ ID NO 10. By all comparable the protein of the prior art inherently anticipates the now claimed invention.

Please Note: The examiner is reading claims 16 and 17 to be composition claims that must contain the recited protein/peptide and a carrier.

(Claim 7, 17, 15, 16) The protein/peptide of CS6 were present in an extract composition).

Inherently the reference anticipates the now claimed invention, as the amino acids sequence of a protein or peptide is an inherent characteristic of the protein or peptide. Atlas Powder Co. V IRECA, 51 USPQ2d 1943, (FED Cir. 1999) states "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art...However, the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new

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to the discoverer. "The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art".

15. Claims 14-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Willshaw et al (reference disclosed in instant specification, page 2, paragraph 5, FEMS Microbiology Letters, vol. 49, pages 473-478, 1988, see seq.align.).

The claimed invention is directed to a peptide of a protein that comprises a sequence from SEQ ID NO 10, wherein the sequence has at least 60% homology to SEQ ID NO 10.

Willshaw et al disclose a peptide of a protein that comprises a sequence that shares 96.6% identity with SEQ ID NO 10, which is at least 60% homology.

The Willshaw peptide shares identity, or a conservative substitution over amino acids 1 to 59, amino acid 61 to 96, amino acid 98 to 106, amino acid 108 to 146 out of the total 146 amino acids of SEQ ID NO 10. The disclosed sequence of Willshaw et al comprises a peptide sequence that codes for a CS6-subunit B (see sequence alignment provided).

The reference anticipates the now claimed invention.

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Conclusion

16. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. .
17. Wolf et al (US Pat. 5,698,416) is cited to show a cloned vector comprising CS6 (see col. 2); Wolf et al, 1989, Vol.57, Infection Immunity, pages 164-173.
18. Askelof et al (US Pat. 5,935,838) is cited to show vaccine compositions the comprise colonization factors from E.coli (see col. 2, lines 1-14).
19. Mekalanos (US Pat. 5,874,088 a continuation of published PCT WO94/01533) is cited to show a mutant strain of Vibrio that expresses colonization factor from E.coli (see claim 19).
20. Knutton, S et al, Infection and Immunity, 1987, is cited to show fimbrial colonization factor antigens from E8775.
21. Grewal, HM et al, Journal of clinical microbiology, May 1994, is cited to show CS6 antigen present in ETEC strains of E.coli.

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22. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
May 9, 2002


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